Introduction – Purpose of a Potency Assay, History

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Assaying Potency of Novel Vaccines: Outline

- From the beginning
- Modern vaccines
- Future needs and prospects

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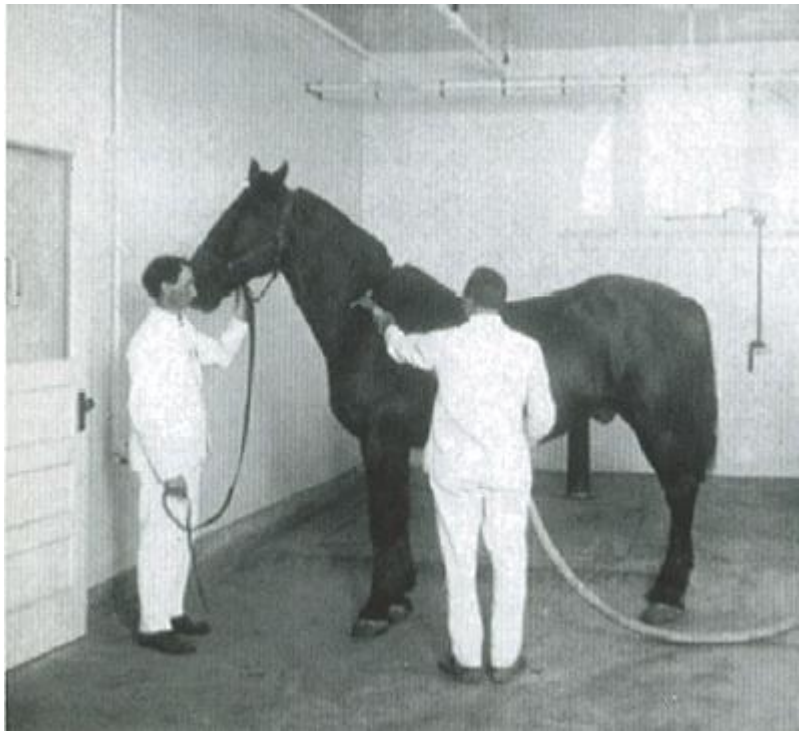
Edward Jenner Prepares to inoculate a young woman, 1802

Production of diphtheria antitoxin



Biologics Control Act

- Passed by Congress on July 1, 1902
- Followed tetanus outbreak with 13 deaths in children given contaminated diphtheria antitoxin in October, 1901
- Authorized Hygienic Laboratory of the Public Health Service to issue regulations:
- To ensure safety, purity and ***potency*** of vaccines, serums, toxins, antitoxins…

Modern Vaccines

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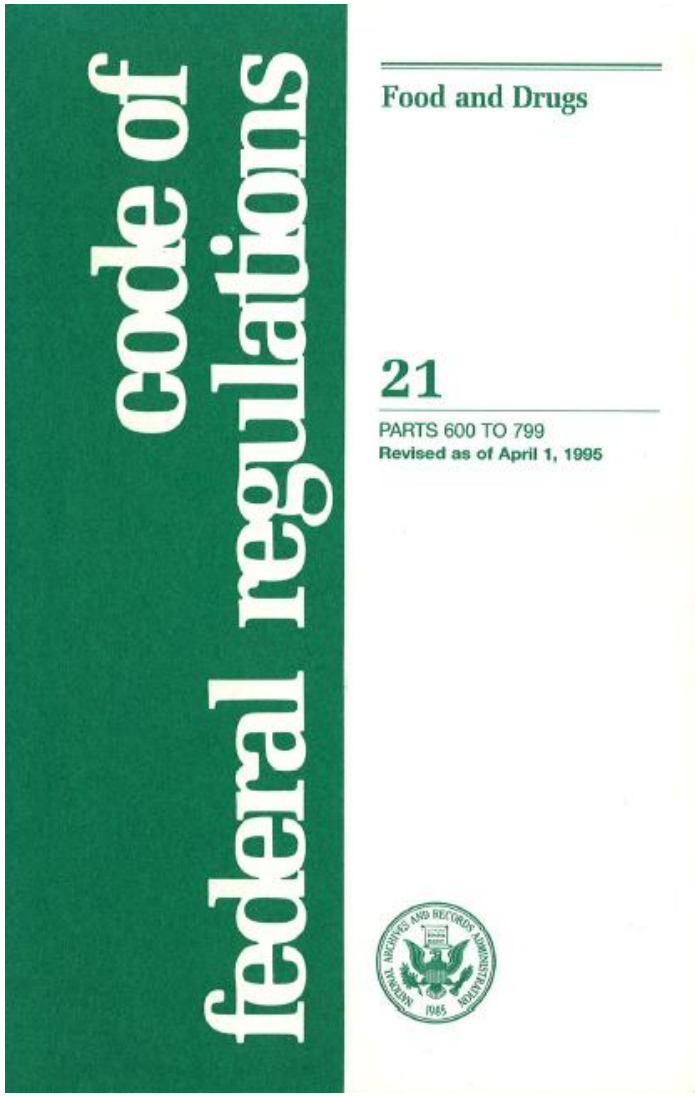
Harry Meyer and Paul Parkman

Code of Federal Regulations 1995



CFR 600.3(s) Definitions (2005)

- The word *potency* is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended to effect a given result.

  and…

CFR 610.10 Potency (2005)

- Tests for potency shall consist of either *in vitro* or *in vivo* tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in CFR 600.3(s) of this chapter.

Existing products for which there are potency tests:

- Live attenuated vaccines, viral, bacterial
- Whole inactivated vaccines, viral, bacterial
- Subunit vaccines, viral, bacterial (including toxoids)
- Multiple serotypes and combinations of above

Established potency test methods:

- Titration of infectious units in live vaccines
- Immune (antibody) responses in animal test systems and/or in humans
- Protection against challenge in animal test systems
- Detailed molecular characterization, e.g., polysaccharides
- Antigen quantitation tests, e.g., flu vaccine

Future needs and prospects

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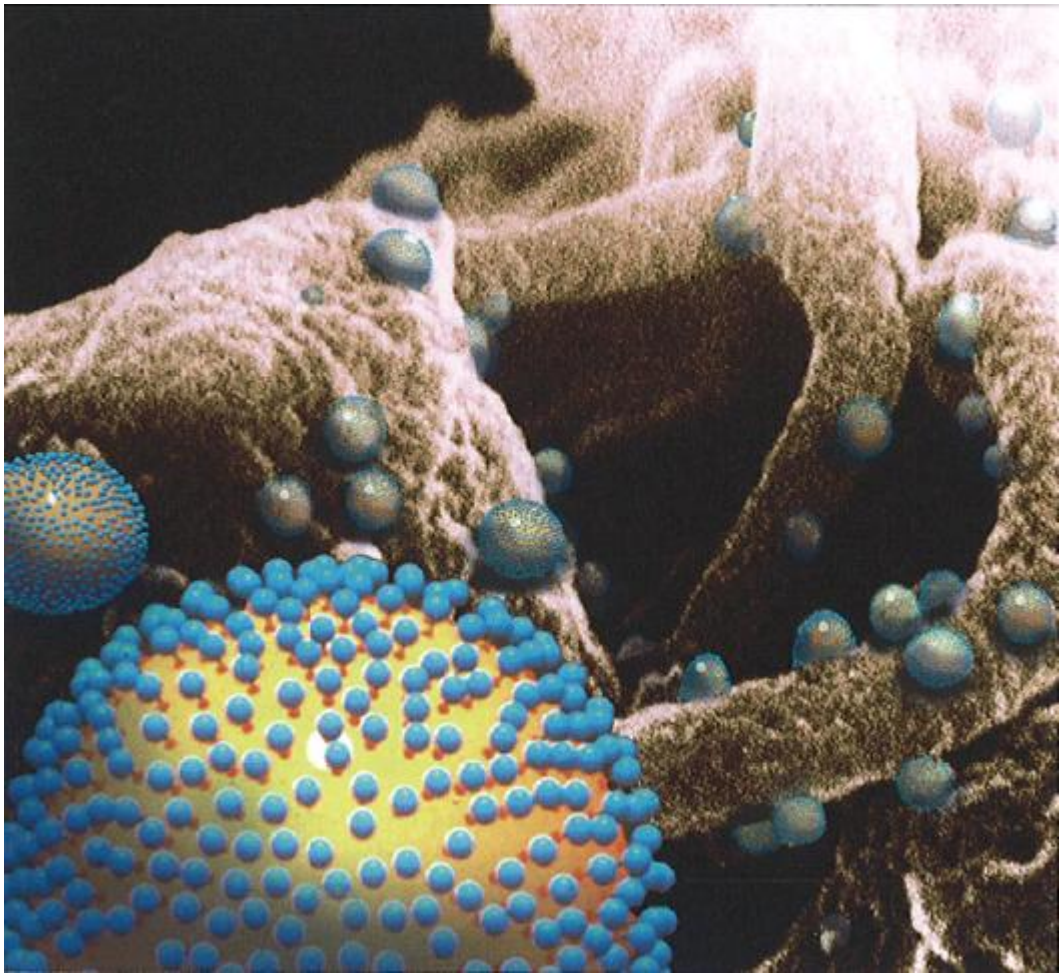
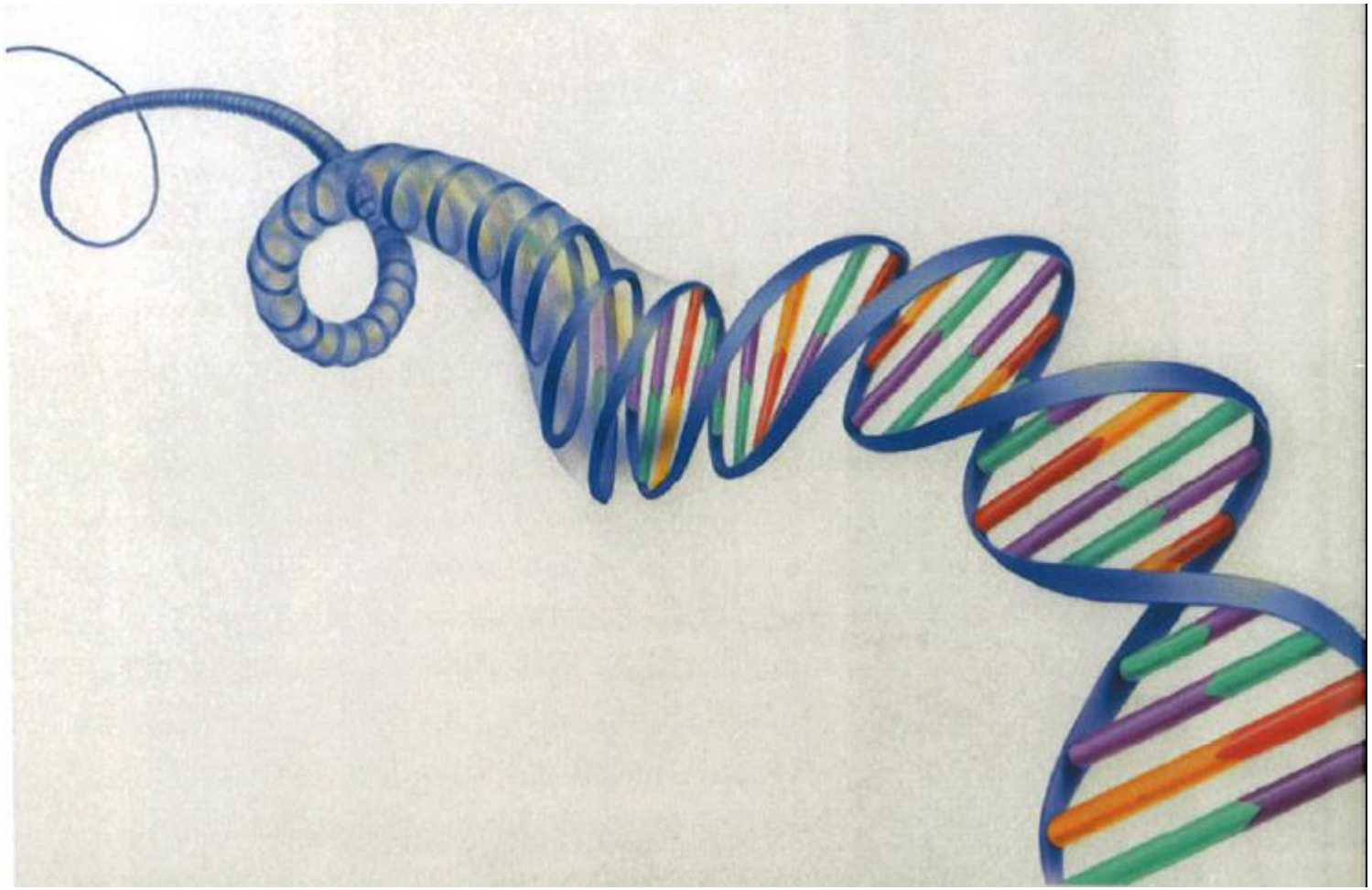
HIV Virus



DNA Molecule



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Potency Assay Issues for Novel Vaccines – a few examples

- Ratio of particle count and infectious unit for recombinant, replication-impaired vectors
- Growth of replication defective vectors in permissive cells, other substrates and *in vivo*
- *In vitro* and *in vivo* transgene expression
  - % of expressing cells
  - copy number per cell

Heterologous Prime-Boost Regimens

Nature Medicine, 2004; 10:1179

Recombinant modified vaccinia virus Ankara expressing antigen 85A boosts BCG-primed and naturally acquired antimycobacterial immunity in humans

Helen McShane[1], Ansar A Pathan[1], Clare R Sander[1], Sheila M Keating[1], Sarah C Gilbert[2], Kris Huygen[3], Helen A Fletcher[1] & Adrian V S Hill[1,3]

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What about assay methods?

- New molecular biological, biochemical and biophysical test methods
- New and refined animal test systems, e.g., knock-outs, imaging
- Cellular immune system mechanisms and assays

Why do we need potency tests?

- Batch manufacturing consistency
- Product stability
- Product performance prediction/assurance
- Product bridging studies
- Evaluate/correlate clinical dose-response
- Avoid product failures or toxicity due to improper potency

Impotency of live-virus vaccines as a result of improper handling in clinical practice

Richard D. Krugman, M.D., Denver, Colo.,*
Barbara C. Meyer, M.S., Joan C. Enterline, M.S.,
Paul D. Parkman, M.D., Rockville, Md.
John J. Witte, M.D., Atlanta, Ga., and
Harry M. Meyer, Jr., M.D., Rockville, Md.

J Pediatrics 1974; 85:512-514.

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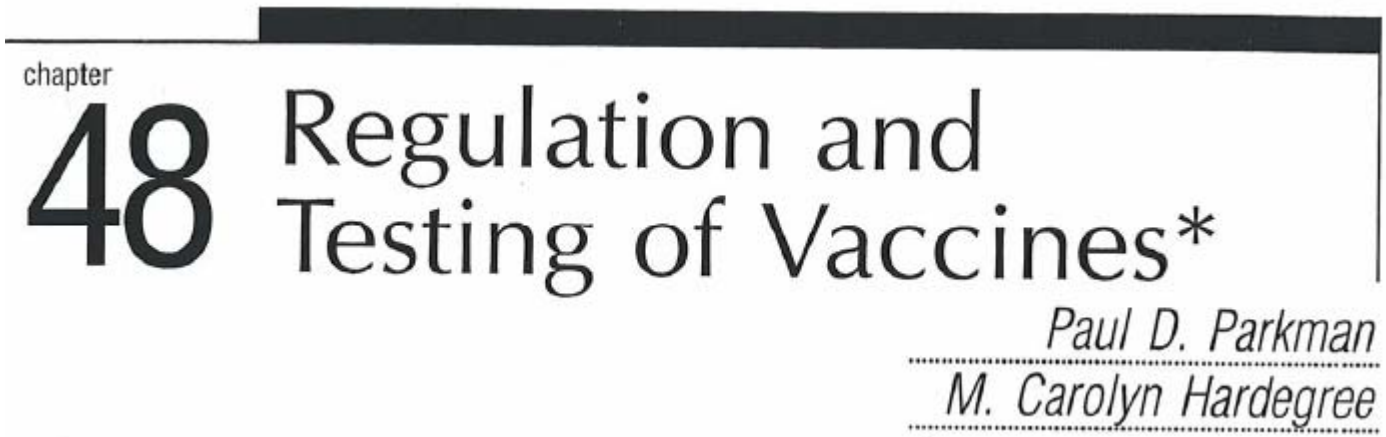

"Among the very first efforts in product development should be explorations of a potency assay. Correlates are sought between the assay results and the preclinical and, later, the clinical testing results."

From PD Parkman, MC Hardegree, Regulation and testing of vaccines, in SA Plotkin and WA Orenstein, *Vaccines*, 3rd edition, Philadelphia, 1999.

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"The final (***POTENCY***) testing methods must be established before the major clinical trials undertaken to demonstrate efficacy and before the manufacture of batches of product that will be used to show a consistent ability to make a product of defined characteristics (i.e., a demonstration of "consistency of manufacture").

From PD Parkman, MC Hardegree, Regulation and testing of vaccines, in SA Plotkin and WA Orenstein, *Vaccines*, 3rd edition, Philadelphia, 1999.